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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/615,854	07/14/2000	Keith L. Black	CEDAR-044569	4523

7590 01/15/2003

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	15

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/615,854	BLACK ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-24,48-55,57-71,135-144,146-160 and 162-189* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-24,48-55,57-71,135-144,146-160 and 162-189* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply* .

DETAILED ACTION

Claims 1-10, 12-24, 48-55, 57-71, 135-144, 146-160, 162-189 are pending in the application.

This Office Action is in response to the Amendment filed on 11/4/02.

Response to Amendment

The rejection of claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160 under 35 U.S.C.112, second paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1-10, 12-24, 48-55, 57-71, 135-144 and 146-160 under 35 U.S.C.112, first paragraph (written description) has been withdrawn in light of Applicants' amendment of the claims.

Claims 1-10, 12-24, 48-55, 57-71, 135-144, 146-160 and newly added claims 162-189 are rejected under 35 U.S.C.112, first paragraph (scope of enablement) for reasons set forth of the record mailed on 5/9/02 and further discussed below.

Claims 57-71 were examined in the prior office action mailed on 5/9/02.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825)

before the application can be examined under 35 U.S.C. §§ 131 and 132. (see attached error report)

Response to Arguments

Claims 1-10, 12-24, 48-55, 57-71, 135-144, 146-160 and 162-189 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a medicant having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to a glioma, ischemia or stroke region in the brain of a mammalian subject by administering a effective amount of Ca dependent K channel activator selecting from the group of YC1 or NONOate by intracarotid infusion simultaneously with the medicant, does not reasonably provide enablement for a method of delivering any medicant to any kind of abnormal brain region by administering Ca dependent potassium channel activator of the guanylyl cyclase activator by any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to the 112 first paragraph (scope of enablement) rejection, Applicants argue that administering in vivo Ca dependent K channel activator increases vascular permeability to the abnormal brain region such that the medicant is selectively delivered to said region. Applicants further indicate that the claimed methods enables a wide variety of medicants having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to more easily penetrate from the lumenel side of the microvasculature to the abluminal side so that they can be delivered selectively to the target cells. Applicants further argue that YC-1 should be include in the scope of the enablement since the specification

provides working examples using this compound. Moreover, Applicants argue that this method is enabled to be applied to delivering medicants to many types of brain abnormalities because the prior art teaches that bradykinin and other Ca dependent K channel activator increases permeability of the neovasculature to many types of brain abnormalities. Applicants also argue that the teaching of Feelisch and the specification enable the skilled artisan to use all kinds of NO donor in this method. Applicants assert that the effective dosage is broad since it is intended to encompass effective doses for any mammal ranging from small to large.

These arguments have considered and deemed partially persuasive. This method while being enabling for delivering a medicant having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to a glioma, ischemia or stroke region in the brain of a mammalian subject by administering a effective amount of Ca dependent K channel activator selecting from the group of YC1 or NONOate by intracarotid infusion simultaneously with the medicant, however, is not enabled for delivering any medicant to any kind of abnormal brain region by administering Ca dependent potassium channel activator of the guanylyl cyclase activator by any route of administration. The scope of the medicant in the claims is very broad. The specification discloses that the medicants encompass therapeutic and diagnostic agents ranging from chemical compounds, peptides, proteins and nucleic acids. The specification teaches that increased the permeability of blood brain barrier (BBB) would enable the passage of molecules having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to more easily penetrate from the lumenel side of the microvasculature to the abluminal side. However, whether molecules lies

outside of this range would be able to cross the BBB is unpredictable. As such, the method is only enabled for delivering medicants within this range.

Applicants' argument regarding YC-1 is considered persuasive. Therefore, YC-1 is enabled for this method.

Applicants' argument that the method is enabled to deliver the medicant to any abnormal brain region is not persuasive. The cited patents (Black, Kozarich and Malfroy-Camine) teach that increased blood brain barrier permeability by intra-carotid infusion of bradykinin and bradykinin analogs. However, these patents do not teach delivering medicants selectively to the abnormal brain region. Therefore, they are not relevant to provide support for the enablement of a method of delivering medicants to an abnormal brain region. Moreover, the prior art does not teach whether other types of brain tumor cells also express Ca dependent K channel. As such, whether a Ca dependent K channel activator can enhance medicant delivery to such abnormal brain region is unpredictable. Applicants' argument that MCA is a model of stroke is accepted. Since the specification and art teach that cells of ischemic brain region and glioma showed increased expression of Ca dependent K channel, this method is enabled for delivering medicant to glioma, stroke and ischemic brain region.

Applicants assert that the teaching of Feelisch and the specification enable the skilled artisan to use all kinds of NO donor in this method. This is considered not persuasive. Contrary to Applicants' assertion, Feelisch reference teaches the complexity and problems in using different classes of NO donor because of their structural differences and pharmacological properties. The specification fails to teach a method to overcome such problems. In addition, the specification only demonstrates that NONOates can enhance BBB permeability. Whether

other classes of NO donor can achieve the same effect is unpredictable. As such, the claimed method is enabled for YC-1 and NONOates.

Applicants' arguments regarding the dosage are accepted. However, the specification only teaches delivering the YC-1 or NONOates by intra-carotid infusion. Whether delivering these compound by other routes such as bolus injection of intravenously, oral or intramuscular injection would achieve the same effect is unpredictable. As such, the method is only enabled for intra-carotid infusion of these compounds.

Based on the limited guidance from art and the specification, one skilled in the art would have to engage undue experimentation to practice the method in commensurate with the claimed scope. Therefore, the method is only enabled for delivering a medicant having a molecular weight between 50 Daltons and about 250 KD or a particle diameter between about 50 to 250 nanometers to a glioma, ischemia or stroke region in the brain of a mammalian subject by administering a effective amount of Ca dependent K channel activator selecting from the group of YC1 or NONOate by intracarotid infusion simultaneously with the medicant.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
January 13, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER